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(54) Title: INHIBITORS OF COPPER-CONTAINING AMINE OXIDASES

(57) Abstract: The present invention is directed to 1,3,4-oxadiazine compounds that function as inhibitors of copper-containg amine oxidases commonly known as semicarbazide-sensitive amine oxidases (SSAO), including the human SSAO known as Vascular Adhesion Protein-1 (VAP-1). These SSAO inhibitors have therapeutic utility as drugs to treat conditions and diseases including, but not limited to, a number of inflammatory conditions and diseases (in particular chronic inflammatory conditions such as chronic arthritis, inflammatory bowel diseases, and chronic skin dermatoses), diseases related to carbohydrate metabolism and to abberations in adipocyte differentiation or function and smooth muscle cell function, and vascular diseases. The compounds have the general formula (I): or a tautomer, isomer, hydrazino alcohol degradation product, or a pharmaceutically acceptable solvate, hydrate, or salt thereof, wherein R^1, R^2, R^3, R^4, R^5,R^6, R^7, and R^8 are as defined her ein.

Inhibitors Of Copper-Containing Amine Oxidases

Field of the Invention

The present invention is in the field of medicinal chemistry and is directed to 1,3,4-oxadiazine compounds and their use as inhibitors of copper-containing amine oxidases (E.C. 1.4.3.6) and enzymes of significant identity thereto. The compounds of the present invention have therapeutic utility as drugs to treat diseases including but not limited to a number of inflammatory conditions and diseases (in particular chronic inflammatory conditions or diseases such as chronic arthritis, inflammatory bowel diseases, and chronic skin dermatoses) as well as diseases related to carbohydrate metabolism and to aberrations in adipocyte differentiation or function and smooth muscle cell function.

Background of the Invention

VAP-1 is a human endothelial cell adhesion molecule that has several unique properties that distinguish it from the other inflammation-related adhesion molecules and these are described as follows. VAP-1 has a unique and restricted expression pattern and mediates lymphocyte binding to vascular endothelium (Salmi, M., and Jalkanen, S., *Science 257*:1407-1409 (1992)). Inflammation induces upregulation of VAP-1 to the surface of vascular endothelial cells mediating leukocyte entry to skin, gut and inflamed synovium (Salmi, M., and Jalkanen, S., *Science 257*:1407-1409 (1992); Salmi, M., *et al., J. Exp. Med 178*:2255-2260 (1993); Arvillomi, A., *et al., Eur. J. Immunol. 26*:825-833 (1996); Salmi, M., *et al., J. Clin. Invest. 99*:2165-2172 (1997)). VAP-1 is rapidly translocated onto vascular endothelium at sites of inflammation. (Salmi, M., and Jalkanen, S., *J. Exp. Med. 183*:569-579 (1996); *J. Exp. Med. 186*:589-600 (1997)). Lastly, VAP-1 has a catalytic extracellular domain with a monoamine oxidase activity (Smith, D.J., *et al., J. Exp. Med. 188*:17-27 (1998)).

The cloning and sequencing of the human VAP-1 cDNA revealed that it encodes a transmembrane protein with homology to a class of enzymes called the copper-containing amine oxidases (E.C. 1.4.3.6). Enzyme assays have shown that VAP-1 possesses a monoamine oxidase (MAO) activity which is present in the extracellular domain of the protein (Smith, D.J., *et al., J. Exp. Med. 188*:17-27 (1998)). Thus, VAP-1 is an ecto-enzyme. Analysis of the VAP-1 MAO activity showed that VAP-1 belongs to the class of membrane-bound MAO's termed semicarbazide-sensitive amine oxidases (SSAO). These are distinguished from the widely distributed mitochondrial MAO-A and B flavoproteins by amino acid sequence, cofactor, substrate specificity and sensitivity to certain inhibitors. However, certain substrates and inhibitors are common to both SSAO and MAO activities. The mammalian SSAO's can metabolize various monoamines produced endogenously or absorbed as dietary or xenobiotic substances. They act principally on primary aliphatic or aromatic monoamines such as methylamine or benzylamine (Lyles, G.A., *Int. J. Biochem. Cell Biol. 28*:259-274 (1996)). Thus, VAP-1 located on the vascular endothelial cell surface can act on circulating primary monoamines with the following reaction pathway.

$$RNH_2 + O_2 + H_2O \longrightarrow RCHO + H_2O_2 + NH_3$$

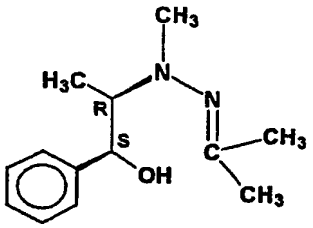
In human clinical tissue samples, expression of VAP-1 is induced at sites of inflammation. This increased level of VAP-1 can lead to increased production of H_2O_2 generated from the action of the VAP-1 SSAO extracellular domain on monoamines present in the blood. This generation of H_2O_2 in the localised environment of the endothelial cell can initiate other cellular events. H_2O_2 is a known signalling molecule that can upregulate other adhesion molecules and this increased adhesion molecule expression may lead to enhanced leukocyte trafficking into areas in which VAP-1 is expressed. Preliminary data supporting this has been obtained using an *in vitro* model in which increased E-Selectin, VCAM-1 and ICAM-1 expression on cultured human umbilical vein endothelial cells (HUVEC) could be observed following addition of purified VAP-1 SSAO protein and benzylamine (an SSAO substrate) to the cell medium. This increase in

adhesion molecule expression was less prominent when mutated (enzymatically inactive) VAP-1 SSAO protein was added instead of the native protein.

A number of 1,3,4-oxadiazines are described in the literature (See, for example, Schmitz, e., *et al.*, *Liebigs Ann. Chem. (6)*:1043-1046 (1983); Samitov, Y.Y., *et al.*, *Zh. Org. Khim. 22(11)*:2271-2277 (1986); Potekhin, A.A., *et al.*, *Khim. Geterotsikl. Soedin. (11)*:1461-1468 (1973); Potekhin, A.A., and Zaitsev, B.D., *Khim. Geterotsikl. Soedin. 7(3)*:301-308 (1971); Ioffe, B.V., and Potekin, A.A., *Tetrahedron Lett. (36)*:3505-3508 (1967); and Kaneko, Japanese Patent Appl. No. 63256951 (1988)). However, use of these compounds as specific SSAO inhibitors apparently has not been disclosed.

In aqueous solution, 1,3,4-oxadiazines may exist in tautomeric hydrazone form. See, for example, Potekhin, A.A., and Zaitsev, B.D., *Khim. Geterotsikl. Soedin. 7(3)*:301-308 (1971), and Ioffe, B.V., and Potekin, A.A., *Tetrahedron Lett. (36)*:3505-3508 (1967).

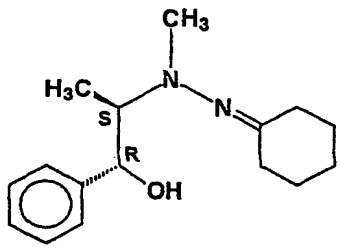
Takahashi, H., *et al.*, *Yakugaku Zasshi 101(12)*:1154-1156 (1981), report the synthesis of a number of *N*-alkylaminoephedrines, including *N*-(isopropylideneamino)-ephedrine (or *R,S*-(+)-(2-hydroxy-1-methyl-2-phenylethyl)methylhydrazone-2-propanone):



These hydrazone compounds were synthesized to evaluate their effect on the bronchial musculature and were found not to exhibit any significant activity. No mention of a 1,3,4-oxadiazine corresponding to the reported hydrazone appears in this reference.

Grifantini, M., *et al.*, *Farmaco, Ed. Sci. 23(3)*:197-203 (1968), report the synthesis of several alkyl- and acyl-derivatives of *N*-amino-1-ephedrine and *N*-amino-d-pseudoephedrine having antidepressant and monoamine oxidase

inhibitory properties. Among the compounds disclosed is the hydrazone erythro-(β-hydroxy-α-methylphenethyl)methylhydrazone cyclohexanone, which has the following structure:



The development of specific VAP-1 SSAO inhibitors that modulate VAP-1 activity would be useful for the treatment of chronic inflammatory conditions or diseases such as chronic arthritis, inflammatory bowel diseases, and chronic skin dermatoses, as well as diseases related to carbohydrate metabolism (including diabetes and complications from diabetes), to aberrations in adipocyte differentiation or function and smooth muscle cell function (in particular, athersclerosis), and to various vascular diseases.

Summary of the Invention

The present invention is broadly directed to the use of 1,3,4-oxadiazine compounds of Formula ***I*** as inhibitors of the class of copper-containing amine oxidases known as semicarbazide-sensitive amine oxidases (SSAO), including the human SSAO known as Vascular Adhesion Protein-1 (VAP-1). As VAP-1 SSAO inhibitors, compounds of the present invention can function to prevent leukocyte adhesion events mediated through SSAO activity. Compounds of the present invention are therefore useful for treating a number of inflammatory conditions and diseases of connective tissue, skin, and the gastrointestinal, central nervous system, and pulmonary systems, including such conditions as chronic arthritis, inflammatory bowel diseases, and chronic dermatoses. The compounds are also useful for treating diseases related to carbohydrate metabolism (such as diabetes),

to aberrations in adipocyte differentiation or function or smooth muscle cell function (such as atherosclerosis and obesity), and to various vascular diseases (such as atheromatous and nonatheromatous ateriosclerosis, ischemic heart disease, and peripheral aterial occlusion).

A further aspect of the present invention is to provide a pharmaceutical composition useful for treating disorders responsive to a decrease in SSAO activity, containing an effective amount of a compound of Formula *I* in a mixture with one or more pharmaceutically acceptable carriers or diluents.

A number of compounds useful in the present invention have not been heretofor reported. Thus, the present invention is also directed to novel 1,3,4-oxadiazines of Formula *I*.

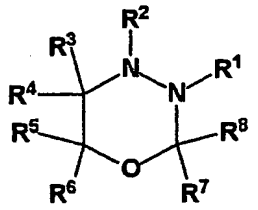
Another embodiment of the present invention is directed to methods for making compounds of Formula *I*.

Detailed Description of the Embodiments

One aspect of the invention is to use a specific group of 1,3,4-oxadiazine compounds having the general formula *I* as defined below, for the manufacture of a pharmaceutical preparation for inhibiting a copper-containing amine oxidase.

Another aspect of the invention is to use a specific group of 1,3,4-oxadiazine compounds having the general formula *I* as defined below, for the manufacture of a pharmaceutical preparation for the treatment of an inflammatory disease or condition, a disease related to carbohydrate metabolism, a disease related to aberrations in adipocyte differentiation or function or smooth muscle cell function, or a vascular disease.

A further aspect of the present invention is directed to a method of inhibiting a copper-containing amine oxidase, contacting said amine oxidase with an inhibitory effective amount of a 1,3,4-oxadiazine compound of Formula *I*:



I

or a tautomer, isomer, hydrazino alcohol degradation product, or a pharmaceutically acceptable solvate, hydrate, or salt thereof; wherein:

R^1 is hydrogen or C_1-C_4 alkyl;

R^2 is hydrogen, C_1-C_4 alkyl, C_2-C_4 alkenyl, aralkyl, C_2-C_6 alkanoyl, C_3-C_6 alkenoyl, C_7-C_{11} or aroyl, which is optionally substituted;

R^3, R^4, R^5, and R^6, which can be the same or different, are hydrogen, C_1-C_4 alkyl or optionally substituted aryl;

or any two of said substituents R^3, R^4, R^5, and R^6 are taken together with the carbon atoms to which they are attached to form an optionally substituted carbocyclic or hetercyclic ring;

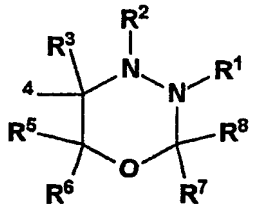
or R^2 and R^3 are taken together with the atoms to which they are attached to form an optionally substituted heterocyclic ring; and

R^7 is hydrogen, C_1-C_4 alkyl, aryl, substituted aryl, heteroaryl, or aralkyl;

R^8 is C_1-C_4 alkyl, aryl, substituted aryl, heteroaryl, or aralkyl or R^7 and R^8 are taken together with the carbon atoms to which they are attached to form an optionally substituted 5-12 membered carbocyclic or heterocyclic ring.

In one embodiment, said contacting occurs *in vitro*. In another embodiment said contacting occurs *in vivo*.

The present invention is directed to methods of treating or preventing inflammatory diseases or conditions using a 1,3,4-oxadiazine of Formula *I*:



I

or a tautomer, isomer, hydrazino alcohol degradation product, isomer, solvate, hydrate, or pharmaceutically acceptable salt thereof; wherein:

R^1 is hydrogen or C_1-C_4 alkyl;

R^2 is hydrogen, C_1-C_4 alkyl, C_2-C_4 alkenyl, aralkyl, C_2-C_6 alkanoyl, C_3-C_6 alkenoyl, or C_7-C_{11} aroyl, which is optionally substituted;

R^3, R^4, R^5, and R^6, which can be the same or different, are hydrogen, C_1-C_4 alkyl or optionally substituted aryl;

or any two of said substituents R^3, R^4, R^5, and R^6 are taken together with the carbon atoms to which they are attached to form an optionally substituted carbocyclic or heterocyclic ring;

or R^2 and R^3 are taken together with the atoms to which they are attached to form an optionally substituted carbocyclic or heterocyclic ring; and

R^7 is hydrogen, C_1-C_4 alkyl, aryl, substituted aryl, heteroaryl, or aralkyl;

R^8 is C_1-C_4 alkyl, aryl, substituted aryl, heteroaryl, or aralkyl;

or R^7 and R^8 are taken together with the carbon atom to which they are attached to form an optionally substituted 5-12 membered carbocyclic or heterocyclic ring.

In one embodiment, the 1,3,4-oxadiazine compounds of Formula *I* are used to treat or prevent connective tissue inflammatory conditions and diseases. In particular, the compounds can be used to treat such conditions or diseases as rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and osteoarthritis.

In another embodiment, the 1,3,4-oxadiazine compounds of Formula *I* are used to treat or prevent gastrointestinal inflammatory conditions and diseases, in particular those such as Crohn's disease, ulcerative colitis, and irritable bowel syndrome.

In yet another embodiment, the 1,3,4-oxadiazine compounds of Formula *I* are used to treat central nervous system inflammatory conditions and diseases, including multiple sclerosis, Alzheimer's disease, and ischaemia-reperfusion injury associated with ischemic stroke.

In another embodiment, the 1,3,4-oxadiazine compounds of Formula *I* are used to treat or prevent pulmonary inflammatory conditions and diseases. In particular, the compounds can be used to treat or prevent such conditions or diseases as asthma and adult respiratory distress syndrome.

In another embodiment, the 1,3,4-oxadiazine compounds of Formula *I* are used to treat or prevent chronic inflammatory skin conditions, especially such inflammatory skin conditions as psoriasis, allegic lesions, lichen planus, and pityriasis rosea.

In yet another embodiment, the 1,3,4-oxadiazine compounds of Formula *I* are used to treat or prevent diseases related to carbohydrate metabolism and complications thereof, such as diabetes and complications from diabetes, microvascular and macrovascular diseases such as atherosclerosis, vascular retinopathies, and neuropathies such as polyneuropathy, mononeuropathies, and autonomic neuropathy.

In still another embodiment, the 1,3,4-oxadiazine compounds of Formula *I* are used to treat or prevent diseases related to or caused by aberrations in adipocyte differentiation or function, such as atherosclerosis or obesity.

In another embodiment, the 1,3,4-oxadiazine compounds of Formula *I* are used to treat or prevent diseases related to or caused by aberrations in smooth muscle cell function, such as athersclerosis.

In another embodiment, the 1,3,4-oxadiazine compounds of Formula *I* are used to treat or prevent vascular diseases, such as atheromatous and

nonatheromatous arteriosclerosis, ischemic heart disease, and Raynaud's Disease and Phenomenon.

Another aspect of the present invention is directed to novel compounds of Formula *I*, as well as tautomers, or pharmaceutically acceptable solvates, hydrates, or salts thereof, as described above;

provided that R^3 and R^4 are not hydrogen or C_1-C_4 alkyl when R^7 and/or R^8 are C_1-C_4 alkyl or optionally substituted phenyl, or when R^7 and R^8 are taken together with the carbon atom to which they are attached for form an unsubstituted C_5-C_7 cycloalkyl group.

The present invention is also directed to pharmaceutical compositions of these novel compounds of Formula *I*, as well as to methods of making the novel compounds.

Preferred compounds are those of Formula *I* wherein R^1 is hydrogen or C_1-C_4 alkyl, preferably hydrogen; and R^2 is hydrogen, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_6-C_{10} ar(C_1-C_4)alkyl, C_2-C_6 alkanoyl, C_2-C_6 alkenoyl, or benzoyl, any of which may be optionally substituted, and R^2 is preferably C_1-C_4 alkyl or optionally substituted benzyl. Preferred substituents for the benzyl group of R^2 are lower alkyl, especially methyl, and nitro, methoxy and halogen, especially chlorine. Especially preferred embodiments of substituted benzyl groups are *p*-toluyl, *p*-nitrobenzyl, *p*-methoxybenzyl, and *p*-chlorobenzyl. Suitable values of R^1 are hydrogen, methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, and *t*-butyl. Suitable values of R^2 include hydrogen, methyl, ethyl, propyl, isopropyl, benzyl, acetyl, benzoyl, *p*-toluyl, *p*-nitrobenzyl, *p*-methoxybenzyl, and *p*-chlorobenzyl.

Preferred compounds of Formula *I* also include those compounds wherein R^3, R^4, R^5 and R^6 , which can be the same or different, are hydrogen, optionally substituted C_1-C_4 alkyl, or optionally substituted phenyl. Preferred substituents for R^3, R^4, R^5 and R^6 are hydrogen and optionally substituted phenyl. Preferred substituted phenyl groups are those substituted with a lower alkyl, especially methyl, or a halogen such as chlorine or fluorine. Especially preferred substituted phenyl groups include *o*-tolyl, *m*-tolyl, *p*-tolyl, *p*-fluorophenyl and *p*-chlorophenyl.

Another group of preferred compounds of Formula *I* are those wherein two of said substituents R^3, R^4, R^5 and R^6 are taken together to form an optionally substituted 5-12 membered carbocyclic or heterocyclic ring.

The ring formed by two of the substituents R^3, R^4, R^5 and R^6 and the carbon atoms to which they are attached is preferably a 5 to 7 membered single ring or a ring to which further rings are condensed (*i.e.*, a ring system). Said 5 to 7 membered ring can be either *cis* or *trans* condensed to the oxadiazine ring, and either spiro or fused. The ring can be heterocyclic or carbocyclic and said ring can be saturated or comprise double bonds. The ring or ring system can be unsubstituted or substituted, wherein the substituent can be alkyl, preferably methyl. Preferably, the ring is a saturated carbocyclic ring. Suitable rings include cyclopentane, cyclohexane, 4-methyl–cyclohexane, cycloheptane or a ring included in the adamantane ring system.

In the case where two of the substituents R^3, R^4 R^5, and R^6 form a ring, then it is preferred that the two remaining substituents are hydrogen.

Another group of preferred compounds are those of Formula *I* in which R^2 and R^3 are taken together to form an optionally substituted heterocyclic ring.

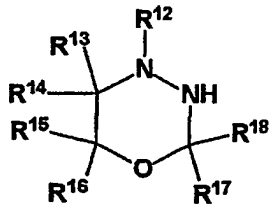
Preferably, the heterocyclic ring formed by the substituents R^2 and R^3 is a 5 to 6 membered nitrogen containing saturated ring. Said ring can be unsubstituted or substituted. According to a preferred embodiment the substituent is alkyl. According to another embodiment, this 5 to 6 membered nitrogen containing ring can be condensed another ring to form a 1,2,3,4-tetrahydroquinoline, 1,2,3,4,-tetrahydroisoquinoline or 2,3-dihydroindole structure. As particularly preferred embodiments can be mentioned piperidine, 1,2,3,4-tetrahydroisoquinoline and 6,7-dimethoxy-1,2,3,4-tetrahydro–isoquinoline.

In the case where R^2 and R^3 together form a heterocyclic ring, then it is preferred that R^4 is hydrogen.

Preferred compounds also include those of Formula *I* in which R^7 and R^8, which can be the same or different, are C_1-C_4 alkyl, or C_6-C_{10} ar(C_1-C_4)alkyl. Preferred values of R^7 and R^8 include C_1-C_4 alkyl, especially methyl and ethyl.

In another group of preferred compounds of Formula *I*, R^7 and R^8 are taken together with the carbon atoms to which they are attached to form an optionally substituted 5-12 membered carbocyclic or heterocyclic ring. The 5-12 membered ring can be saturated or unsaturated carbocyclic or heterocyclic and said ring can be unsubstituted or substituted. The substituent can be alkyl, aralkyl, or substituted aralkyl. An especially preferred substituent is benzyl. Saturated rings are preferable. A particularly preferable spiro-condensed ring is N-benzylpiperidine.

A preferred subgenus of compounds has Formula **Ia**:



Ia

or a tautomer, isomer, or a pharmaceutically acceptable solvate, hydrate, or salt thereof, wherein:

R^{12} is hydrogen, C_1-C_4 alkyl or phenyl(C_1-C_3)alkyl;

R^{13} is hydrogen, C_1-C_4 alkyl or phenyl; or

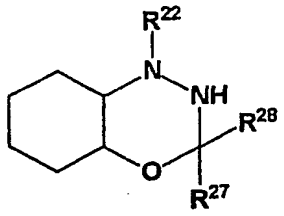
R^{15} is hydrogen or C_1-C_4 alkyl;

R^{13} and R^{15} are taken together with the carbon atoms to which they are attached to form a five to seven membered cycloalkyl ring;

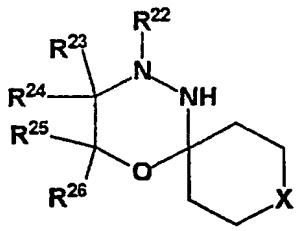
R^{14} and R^{16} are independently hydrogen or C_1-C_4 alkyl; and

R^{17} is C_1-C_4 alkyl, and R^{18} is C_1-C_4 alkyl, or R^{17} and R^{18} are taken together with the carbon atom to which they are attached to form a five or six membered saturated ring optionally including one ring nitrogen (NR^{19}) where R^{19} is hydrogen, C_1-C_4 alkyl or phenyl(C_1-C_3)alkyl.

Other preferred sub-genuses of the present invention are compounds having either Formula **Ib** or Formula **Ic**:



Ib



Ic

or a tautomer, isomer, or a pharmaceutically acceptable solvate, hydrate, or salt thereof, wherein:

R^{22} is hydrogen, C_1-C_4 alkyl or benzyl, preferably methyl or benzyl;

R^{23} is hydrogen or C_1-C_4 alkyl, preferably hydrogen or methyl;

R^{24} is hydrogen or C_1-C_4 alkyl;

R^{25} is hydrogen, C_1-C_4 alkyl or phenyl, preferably hydrogen or phenyl;

R^{26} is hydrogen or C_1-C_4 alkyl;

R^{27} is C_1-C_4 alkyl;

R^{28} is C_1-C_4 alkyl; and

X is a covalent bond, $-CH_2-$ or $-NR^{19}-$, where R^{19} is hydrogen, C_1-C_4 alkyl or benzyl.

Examples of compounds of, and useful in, the present invention include:

9-benzyl-2-methyl-5-oxa-1,2,9-triazaspiro[5.5]undecane;

9-benzyl-2-methyl-4-phenyl-5-oxa-1,2,9-triazaspiro[5.5]-undecane;

(3*S*,4*R*)-9-benzyl-2,3-dimethyl-4-phenyl-5-oxa-1,2,9-triazaspiro[5.5]undecane;

(3*R*,4*S*)-2,3-dimethyl-4-phenyl-5-oxa-1,2-diazaspiro[5.5]undecane;

(4a*R**,8a*S**)-4-methyl-2,2-pentamethylene-3,4,4a,5,6,7,8,8a-octahydro-2*H*-1,3,4-benzoxadiazine;

(4a*R**,8a*R**)-2,2,4-trimethyl-3,4,4a,5,6,7,8,8a-octahydro-2*H*-1,3,4-benzoxadiazine;

(4a*R**,8a*R**)-4-benzyl-2-ethyl-2-methyl-3,4,4a,5,6,7,8,8a-octahydro-2*H*-1,3,4-benzoxadiazine; and

2,2-dimethyl-1,2,4a,5-tetrahydro-4*H*,10*H*-1,3,4-oxadiazino[4,5-*b*]isoquinoline; as well as pharmaceutically acceptable salts thereof, including, for example, hydrochloride or dihydrochloride salts.

The term "alkyl" as employed herein by itself or as part of another group refers to both straight and branched chain radicals of up to 12 carbons, such as methyl, ethyl, propyl, isopropyl, butyl, *t*-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl, dodecyl. For example, C_1-C_4 alkyl is a straight or branched alkyl and thus can include methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, *tert*-butyl and isobutyl.

The term "alkenyl" is used herein to mean a straight or branched chain radical of 2-20 carbon atoms, unless the chain length is limited thereto, including, but not limited to, ethenyl, 1-propenyl, 2-propenyl, 2-methyl-l-propenyl, 1-butenyl, 2-butenyl, and the like. Preferably, the alkenyl chain is 2 to 10 carbon atoms in length, more preferably, 2 to 8 carbon atoms in length most preferably from 2 to 4 carbon atoms in length.

The term "aryl" as employed herein by itself or as part of another group refers to monocyclic or bicyclic aromatic groups containing from 6 to 12 carbons in the ring portion, preferably 6-10 carbons in the ring portion, such as phenyl, naphthyl or tetrahydronaphthyl.

The term "aralkyl" as employed herein should be interpreted as any aryl attached to the alkyl, which is a chain of 1 to 6 carbon atoms and which in turn can be straight or branched. Preferably, the chain contains 1 to 3 carbon atoms. A preferred aryl group is phenyl, which can be substituted or unsubstituted. Preferable substituents are lower alkyl (*i.e.*, C_1-C_4 alkyl), especially methyl, or a halogen. As particular preferred embodiments can be mentioned benzyl, *p*-methylbenzyl, *p*-chlorobenzyl, 2-phenylethyl and 3-phenylpropyl.

The term "alkanoyl" as employed herein refers to a carbonyl moiety to which is attached any of the above alkyl groups. For example, the term "C_2-C_6 alkanoyl" includes, but is not limited to, ethanoyl, propanoyl, butanoyl, 2-methyl-propanoyl, pentanoyl, hexanoyl.

The term "alkenoyl" is used herein to mean a carbonyl moiety to which is attached any of the above alkenyl groups. For example, the term "C_2-C_6 alkenoyl" refers to, but is not limited to, ethenoyl, 1-propenoyl, 2-propenoyl, 2-methyl-1-propenoyl, 1-butenoyl, 2-butenoyl, and the like. Preferably, the alkenyl chain is 2 to 10 carbon atoms in length, and more preferably, 2 to 6 carbon atoms in length.

The term "carbocyclic ring" as employed herein by itself or as part of another group refers to a monocyclic or bicyclic aromatic ring or ring system containing from 6 to 12 carbons in the ring portion, as defined above, or to any 3- to 9-membered mono- or 7- to 10-membered bicyclic carbon ring system, any ring of which may be saturated or unsaturated. Typical examples include phenyl, naphthyl, and cyclohexyl.

The term "heterocyclic ring" as used herein represents a stable 5- to 7-membered mono- or bicyclic or stable 7- to 12-membered bicyclic heterocyclic ring system any ring of which may be saturated or unsaturated, and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of N, O and S, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. Especially useful are rings containing one oxygen or sulfur, one to three nitrogen atoms, or one oxygen or sulfur combined with one or two nitrogen atoms. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heterocyclic groups include piperidinyl, piperazinyl, N-benzylpiperidine, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, quinuclidinyl, isothiazolidinyl, indolyl, quinolinyl, isoquinolinyl, chromanyl, benzimidazolyl, thiadiazoyl, benzopyranyl, benzothiazolyl, benzo[b]thiophenyl, benzo[2,3-c]1,2,5-oxadiazolyl, benzoxazolyl, furyl, tetrahydrofuryl, tetrahydropyranyl, thienyl, benzothienyl,

thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, and oxadiazolyl. Morpholino is the same as morpholinyl.

The term "heteroaryl" as employed herein refers to groups having 5 to 14 ring atoms; 6, 10 or 14 B electrons shared in a cyclic array; and containing carbon atoms and 1, 2 or 3 oxygen, nitrogen or sulfur heteroatoms (where examples of heteroaryl groups are: thienyl, benzo[b]thienyl, naphtho[2,3-b]thienyl, thianthrenyl, furyl, pyranyl, isobenzofuranyl, benzoxazolyl, chromenyl, xanthenyl, phenoxathiinyl, 2*H*-pyrrolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolizinyl, isoindolyl, 3*H*-indolyl, indolyl, indazolyl, purinyl, 4*H*-quinolizinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinazolinyl, cinnolinyl, pteridinyl, 4α*H*-carbazolyl, carbazolyl, β-carbolinyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, phenazinyl, isothiazolyl, phenothiazinyl, isoxazolyl, furazanyl and phenoxazinyl groups).

The term "halogen" or "halo" as employed herein by itself or as part of another group refers to chlorine, bromine, fluorine or iodine, with chlorine being preferred.

The term "substituted" unless otherwise provided for herein, refers to one or more groups independently selected from the group consisting of halo, halo (C_{1-6})alkyl, ar(C_{1-6})alkyl, aryl, nitro, C_{1-6} alkoxy, and C_{1-6} alkyl as long as the resulting compound is stable. Preferred optional substituents include: halo, ar(C_{1-6})alkyl, aryl, and C_{1-6} alkyl.

The term "cycloalkyl" as employed herein by itself or as part of another group refers to cycloalkyl groups containing 3 to 9 carbon atoms. Typical examples are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and cyclononyl.

The term "hydroxyalkyl" as employed herein refers to any of the above alkyl groups substituted by one or more hydroxyl moieties.

The term "carboxyalkyl" as employed herein refers to any of the above alkyl groups substituted by one or more carboxylic acid moieties.

The term "haloalkyl" as employed herein refers to any of the above alkyl groups substituted by one or more chlorine, bromine, fluorine or iodine with fluorine and chlorine being preferred, such as chloromethyl, iodomethyl, trifluoromethyl, 2,2,2-trifluoroethyl, and 2-chloroethyl.

The term "haloalkoxy" as used herein refers to any of the above haloalkyl groups bonded to an oxygen atom, such as trifluromethoxy, trichloromethoxy, and the like.

The term "alkoxy" is used herein to mean a straight or branched chain radical of 1 to 20 carbon atoms, unless the chain length is limited thereto, bonded to an oxygen atom, including, but not limited to, methoxy, ethoxy, *n*-propoxy, isopropoxy, and the like. Preferably the alkoxy chain is 1 to 10 carbon atoms in length, more preferably 1 to 8 carbon atoms in length.

The compounds of the invention will in general exist in equilibrium with their other tautomeric forms. For example, compounds of Formula *I* may exist in solution as mixtures of ring (**Id**) and chain (**Ie**) tautomers:

Id **Ie**

wherein R^1-R^8 are as defined above. It is to be understood that all tautomeric forms of the compounds of Formula *I*, as well as all possible mixtures thereof, are included within the scope of the present invention.

There is evidence that it is the hydrazino alcohol form of the disclosed compounds that binds to VAP-1 and inhibits its SSAO activity. Thus, it is to be further understood that such hydrazino alcohol degradation products of the disclosed compounds are to be included within the scope of the compounds of Formula *I* when they are used to inhibit VAP-1 SSAO activity and to treat the various VAP-1 mediated diseases and conditions described herein.

Some of the compounds disclosed herein may contain one or more

asymmetric centers and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms. The present invention is also meant to encompass racemic mixtures, resolved forms and mixtures thereof, as well as the individual enantiomers that may be separated according to methods that are well know to those of ordinary skill in the art. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended to include both E and Z geometric isomers.

As used herein, the term "stereoisomers" is a general term for all isomers of individual molecules that differ only in the orientation of their atoms in space. It includes enantiomers and isomers of compounds with more than one chiral center that are not mirror images of one another (diastereomers).

The term "asymmetric center" or "chiral center" refers to a carbon atom to which four different groups are attached.

The term "enantiomer" or "enantiomeric" refers to a molecule that is nonsuperimposeable on its mirror image and hence optically active wherein the enantiomer rotates the plane of polarized light in one direction and its mirror image rotates the plane of polarized light in the opposite direction.

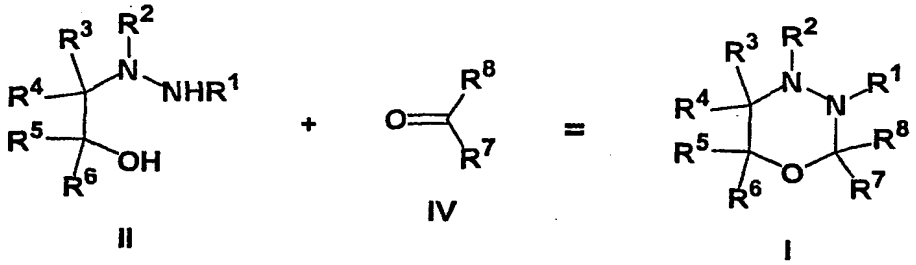
The term "racemic" refers to a mixture of equal parts of enantiomers and which is optically inactive.

The term "resolution" refers to the separation or concentration or depletion of one of the two enantiomeric forms of a molecule. The phrase "enantiomeric excess" refers to a mixture wherein one enantiomer is present is a greater concentration than its mirror image molecule.

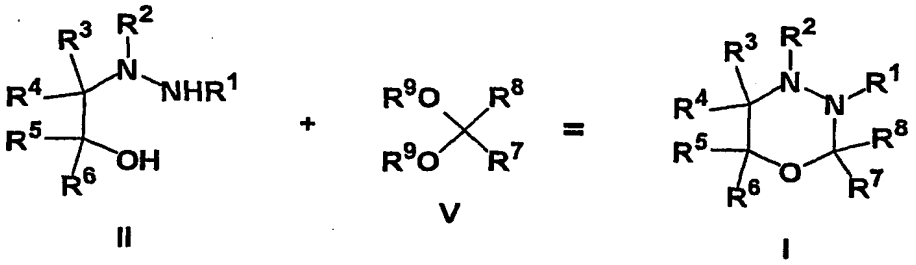
When any variable occurs more than one time in any constituent or in Formula *I*, its definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

Another aspect of the present invention is directed to methods for preparing compounds of Formula *I*. The compounds of the present invention can be prepared by one of the following routes.

Synthesis of the compounds of Formula *I* (compounds **I**) starts from hydrazino alcohols **II** and uses ketones **IV** or ketone equivalents, *e.g.* acetals **V** (R^9 is preferably a methyl or ethyl group), as condensing agents.



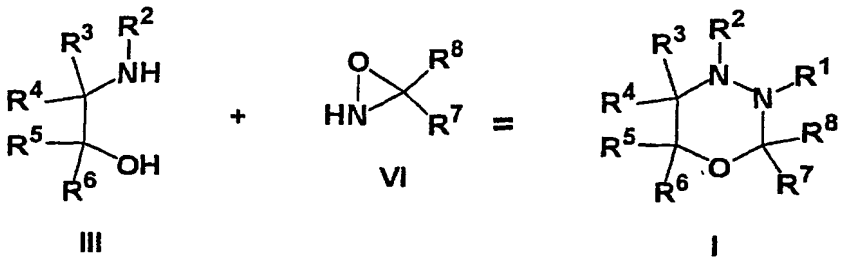
II + IV = I



II + V = I

Condensations are performed at 20-120 °C, with or without acidic or basic catalysts, or adsorbents of water. Illustrative examples of "acidic catalysts" are hydrochloric, *p*-toluenesulfonic, acetic, and tartaric and oxalic acids. An "acidic catalyst" may also include any strongly acid resin ion-exchange resin suitable for non-aqueous catalysis, such as Amberlist® 15. An illustrative example of "a basic catalyst" is triethylamine. The term "water adsorbent" includes dried magnesium sulfate, silica and molecular sieve 4Å.

An alternative procedure for the synthesis of compounds **I** uses amino alcohols **III** and oxaziridines **VI** (Schmitz, E., *et al.*, *Liebigs Ann. Chem.*:1043-1046 (1983)).

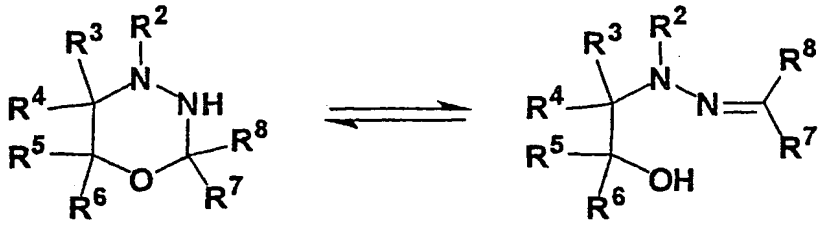


III VI I

Hydrazino alcohols **II** are known from the literature or can be prepared following the literature processes by starting from amino alcohol precursors **III** (Taguchi, T. *et al., J. Org. Chem. 29*:1097-1103 (1964); Takahashi, H., *et al., Chem. Pharm. Bull. 39*:836-842 (1991); Shen, J.K., *et al., J. Chem. Soc., Perkin Trans. 1*:2087-2097 (1993); Rosling, A., *et al., Heterocycles 45*:95-106 (1997); Rosling, A., *et al., J. Chem. Res.(S)*:492 (1998); *J. Chem. Res.(M)*:2237-2250 (1998)). In the cases $R^3 \neq R^4$ and $R^5 \neq R^6$, hydrazino alcohols **II** are used as single diastereomers. The synthesis of the enantiomers of compounds **I** starts from enantiomerically pure hydrazino alcohols **II**, which are known from the literature or can be prepared following the literature processes (Trepanier, D.L., *et al, J. Org. Chem. 29*:668-672 (1964)). Condensations occur without racemization. Enantiomerically pure products **I** can also be prepared by standard enantiomer separation techniques from the racemates of **I**.

For compounds **I** in which $R^7 \neq R^8$ and $R^3 \neq R^4$ or $R^5 \neq R^6$, geometric isomerism is possible. Diastereomers formed in condensations can be separated, if necessary, by standard organic separation methods.

The compounds of this invention are useful in the form of acid addition salts. The expression "pharmaceutically acceptable acid addition salt" is intended to apply to any non-toxic organic and inorganic acid addition salts of the base compounds of Formula *I*. Illustrative inorganic acids which form suitable salts include hydrochloric, hydrobromic, sulfuric and phosphoric acids. Illustrative organic acids which form suitable salts include acetic, lactic, malonic, succinic, glutaric, fumaric, malic, tartaric, citric, ascorbic, maleic, benzoic, phenylacetic, cinnamic and salicylic acids



Id Ie

Compounds **I** exist in solution as mixtures of ring (**Id**) and chain (**Ie**) tautomers. The equilibria exhibit a strong dependence on the substituents and the solvents used (Dorman, L.C., *J. Org. Chem. 29*:255-260 (1967); Potekhin, A.A. and Zaitsev, B.D., *Chem. Heterocyclic Compounds 7*:277-301 (1971); Potekhin, A.A. and Bogankova, E.A., *Chem. Heterocyclic Compounds 9*:1321-1461 (1973); Valters, R.E., *et al., Adv. Heterocyclic Chem. 66*:1-71 (1996)). On the other hand, crystals of hydrochloride salts of **I** exist individually in ring form, as proved by solid-state NMR measurements.

The present invention provides a method of treating VAP-1 mediated conditions by selectively inhibiting VAP-1 SSAO activity, which method comprises administering to an animal in need thereof a therapeutically effective amount of a compound selected from the class of compounds depicted by Formula *I*, wherein one or more compounds of Formula *I* is administered in association with one or more non-toxic, pharmaceutically acceptable carriers and/or diluents and/or adjuvants and if desired other active ingredients.

The compounds of the present invention can be used to treat inflammatory conditions and diseases including but not limited to connective tissue inflammatory conditions and diseases such as ankylosing spondylitis, Reiter's syndrome, psoriatic arthritis, osteoarthritis or degenerative joint disease, rheumatoid arthritis, Sjögren's syndrome, Behçet's syndrome, relapsing polychondritis, systemic lupus erythematosus, discoid lupus erythematosus, systemic sclerosis, eosinophilic fasciitis, polymyositis and dermatomyositis, polymyalgia rheumatica, vasculitis, temporal arteritis, polyarteritis nodosa, Wegener's granulomatosis, mixed connective tissue disease, and juvenile rheumatoid arthritis; gastrointestinal inflammatory conditions and diseases such as Crohn's disease, ulcerative colitis,

irritable bowel syndrome (spastic colon), fibrotic conditions of the liver, inflammation of the oral mucosa (stomatitis), and recurrent aphtous stomatitis; central nervous system inflammatory conditions and diseases such as multiple sclerosis, Alzheimer's disease, and ischaemia-reperfusion injury associated with ischemic stroke; pulmonary inflammatory conditions and diseases such as asthma, chronic obstructive pulmonary disease, and adult respiratory distress syndrome; and skin inflammatory conditions and diseases such as contact dermatitis, atopic dermatitis, psoriasis, pityriasis rosea, lichen planus, and pityriasis rubra pilaris.

Moreover, the compounds of the invention can be used to treat diseases related to carbohydrate metabolism and complications thereof, such as diabetes and complications of diabetes including, but not limited to microvascular and macrovascular disease such as atherosclerosis, vascular retinopathies, retinopathy; nephropathy and nephrotic syndrome, neuropathies such as polyneuropathy, mononeuropathies, and autonomic neuropathy, and foot ulcers and joint problems, as well as increased risk of infection; diseases related to or caused by aberrations in adipocyte differentiation or function such as atherosclerosis and obesity; and vascular diseases such as atheromatous and nonatheromatous ateriosclerosis, ischemic heart disease including myocardial infarction, peripheral aterial occlusion, thromboangiitis obliterans (Buerger's disease), and Raynaud's disease and phenomenon.

In particular, the present compounds can be used to treat atherosclerosis. It is known that VAP-1 is expressed on adipocytes, smooth muscle cells, endothelial cells and is related to inflammation. Atherosclerotic plaque consists of accumulated intracellular and extracellular lipids, smooth muscle cells, connective tissue, and glycosaminoglycans. The earliest detectable lesion of atherosclerosis is the fatty streak (consisting of lipid-laden foam cells, which are macrophages that have migrated as monocytes from the circulation into the subendothelial layer of the intima), which later evolves into the fibrous plaque (consisting of intimal smooth muscle cells surrounded by connective tissue and intracellular and extracellular lipids).

The term "treat inflammation" is intended to include the administration of compounds of the present invention to a subject for purposes, which can include prophylaxis, amelioration, prevention or cure of an inflammatory condition or disease. Such treatment need not necessarily completely ameliorate the inflammatory condition or disease. Further, such treatment can be used in conunction with other traditional treatments for reducing the inflammatory condition known to those of skill in the art.

The compounds of the present invention may be administered in an effective amount within the dosage range of about 0.1 μg/kg to about 300 mg/kg, preferably between 1.0 μg/kg to 10 mg/kg body weight. Compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily.

The pharmaceutical compositions of the present invention can be administered to any animal that can experience the beneficial effects of the compounds of the invention. Foremost among such animals are humans, although the invention is not intended to be so limited.

The pharmaceutical compositions of the present invention can be administered by any means that achieve their intended purpose. For example, administration can be by parenteral, subcutaneous, intravenous, intramuscular, intraperitoneal, or intradermal injections, or by transdermal, buccal, or ocular routes. Alternatively, or concurrently, administration can be by the oral route. Particularly preferred is oral administration. The dosage administered will be dependent upon the age, health, and weight of the recipient, kind of concurrent treatment, if any, frequency of treatment, and the nature of the effect desired.

In addition to the pharmacologically active compounds, the pharmaceutical preparations of the compounds can contain suitable pharmaceutically acceptable carriers comprising excipients and auxiliaries that facilitate processing of the active compounds into preparations that can be used pharmaceutically. The pharmaceutical preparations of the present invention are manufactured in a manner that is, itself, known, for example, by means of conventional mixing, granulating,

dragee-making, dissolving, or lyophilizing processes. Thus, pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid excipients, optionally grinding the resulting mixture and processing the mixture of granules, after adding suitable auxiliaries, if desired or necessary, to obtain tablets or dragee cores.

Suitable excipients are, in particular, fillers such as saccharides, for example, lactose or sucrose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example, tricalcium phosphate or calcium hydrogen phosphate, as well as binders, such as starch paste, using, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, tragacanth, methyl cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, and/or polyvinyl pyrrolidone. If desired, disintegrating agents can be added, such as the above-mentioned starches and also carboxymethyl-starch, cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof, such as sodium alginate. Auxiliaries are, above all, flow-regulating agents and lubricants, for example silica, talc, stearic acid or salts thereof, such as magnesium stearate or calcium stearate, and/or polyethylene glycol. Dragee cores are provided with suitable coatings, that, if desired, are resistant to gastric juices. For this purpose, concentrated saccharide solutions can be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, polyethylene glycol, and/or titanium dioxide, lacquer solutions and suitable organic solvents or solvent mixtures. In order to produce coatings resistant to gastric juices, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate, are used. Dye stuffs or pigments can be added to the tablets or dragee coatings, for example, for identification or in order to characterize combinations of active compound doses.

Other pharmaceutical preparations that can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer such as glycerol or sorbitol. The push-fit capsules can contain the active compounds in the form of granules that may be mixed with fillers such as lactose, binders such as starches, and/or lubricants such as talc or magnesium

stearate and, optionally, stabilizers. In soft capsules, the active compounds are preferably dissolved or suspended in suitable liquids such as fatty oils or liquid paraffin. In addition, stabilizers may be added.

Suitable formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form, for example water-soluble salts and alkaline solutions. Especially preferred alkaline salts are ammonium salts prepared, for example, with Tris, choline hydroxide, bis-Tris propane, N-methylglucamine, or arginine. In addition, suspensions of the active compounds as appropriate oily injection suspensions can be administered. Suitable lipophilic solvents or vehicles include fatty oils, for example, sesame oil, or synthetic fatty acid esters, for example, ethyl oleate or triglycerides or polyethylene glycol-400 (the compounds are soluble in PEG-400). Aqueous injection suspensions can contain substances that increase the viscosity of the suspension, for example sodium carboxymethyl cellulose, sorbitol, and/or dextran. Optionally, the suspension may also contain stabilizers.

The following examples are illustrative, but not limiting, of the method and compositions of the present invention. Other suitable modifications and adaptations of the variety of conditions and parameters normally encountered and obvious to those skilled in the art are within the spirit and scope of the invention.

Example 1

9-Benzyl-2-methyl-5-oxa-1,2,9-triazaspiro[5.5]undecane dihydrochloride

The title compound was synthesized using each of the following three synthetic methods.

Method 1a: To a solution of 2-(N^1-methylhydrazino)ethanol (0.30 g, 3.3 mmol) in dry toluene (10 ml), 1-benzylpiperidin-4-one (0.63 g, 3.3 mmol) was added and the reaction mixture was left to stand at room temperature for 24 hours. The toluene solution was decanted from the separated droplets of water and evaporated to dryness. Evaporation was repeated after the addition of dry

toluene (10 ml). The pale-yellow oily product was dissolved in ethanol (2 ml) and was converted to the crystalline dihydrochloride salt by using ethanol containing 22% hydrogen chloride (1 ml) and diethyl ether. The crystals were filtered off and recrystallized from ethanol/diethyl ether. ^{13}C-NMR (500 MHz, solid state): δ 26.61, (broad), 33.81, 44.1, 52.2, 57.93, 83.44 (C-2), 128.42, 130.0, 133.04.

Method 1b: To a solution of 2-(*N*^{1}-methylhydrazino)ethanol (0.30 g, 3.3 mmol) in dry toluene (10 ml), 1-benzylpiperidin-4-one (0.63 g, 3.3 mmol) was added. The reaction mixture was refluxed for 5 hours and then evaporated to dryness. Evaporation was repeated after the addition of dry toluene (10 ml). The pale-yellow oily product was dissolved in ethanol (2 ml) and was converted to the crystalline dihydrochloride salt by using ethanol containing 22% hydrogen chloride (1 ml) and diethyl ether. The crystals were filtered off and recrystallized from ethanol/diethyl ether. ^{13}C-NMR: see Method 1a.

Method 1c: To a solution of 2-(*N*^{1}-methylhydrazino)ethanol (0.30 g, 3.3 mmol) in dry toluene (10 ml), 1-benzylpiperidin-4-one (0.63 g, 3.3 mmol) was added. The reaction mixture was refluxed for 5 hours in a Dean-Stark apparatus and then evaporated to dryness. The oily residue was dissolved in ethanol (2 ml) and was converted to the crystalline dihydrochloride salt by using ethanol containing 22% hydrogen chloride (1 ml) and diethyl ether. The crystals were filtered off and recrystallized from ethanol/diethyl ether. ^{13}C-NMR: see Method 1a.

Example 2

9-Benzyl-2-methyl-4-phenyl-5-oxa-1,2,9-triazaspiro[5.5]undecane dihydrochloride

The title compound was synthesized using each of the following two synthetic methods.

Method 2a: To a solution of 2-(*N*^{1}-methylhydrazino)-1-phenylethanol (0.50 g, 3 mmol) in dry toluene (25 ml), 1-benzylpiperidin-4-one (0.57 g, 3 mmol) and a catalytic amount (1 drop) of glacial acetic acid were added. The reaction mixture was left to stand at room temperature for 24 hours and then evaporated to dryness. Evaporation was repeated after the addition of dry toluene (10 ml). The

pale-yellow oily product was dissolved in ethanol (2 ml) and was converted to the crystalline dihydrochloride salt by using ethanol containing 22% hydrogen chloride (1 ml) and diethyl ether. The crystals were filtered off and recrystallized from ethanol/diethyl ether. ^{13}C-NMR (500 MHz, solid state): δ 26.61, (broad), 33.81, 44.1, 52.2, 57.93, 83.44 (C-2), 128.42, 130.0, 133.04.

Method 2b: To a solution of 2-(N^1-methylhydrazino)-1-phenylethanol (0.50 g, 3 mmol) in dry toluene (25 ml), 1-benzylpiperidin-4-one (0.57 g, 3 mmol) and a catalytic amount (1 drop) of triethylamine were added. The reaction mixture was left to stand at room temperature for 24 hours and then evaporated to dryness. Evaporation was repeated after the addition of dry toluene (10 ml). The pale-yellow oily product was dissolved in ethanol (2 ml) and was converted to the crystalline dihydrochloride salt by using ethanol containing 22% hydrogen chloride (1 ml) and diethyl ether. The crystals were filtered off and recrystallized from ethanol/diethyl ether. ^{13}C-NMR: see Method 2a.

Example 3

(3S,4R)-9-Benzyl-2,3-dimethyl-4-phenyl-5-oxa-1,2,9-triazaspiro[5.5]undecane dihydrochloride

The title compound was synthesized using each of the following two synthetic methods.

Method 3a: To a solution of (1*R*,2*S*)-*N*-aminoephedrine (0.30 g, 1.7 mmol) in dry benzene (30 ml), 1-benzylpiperidin-4-one (0.31 g, 1.6 mmol) was added. The reaction mixture was left to stand at room temperature for 6 hours, and then evaporated to dryness. The residue was dissolved in 5 ml ethanol containing 22% hydrogen chloride after a few minutes the solution was evaporated to dryness, and the residue was crystallized from an ethanol/diethyl ether mixture. ^{13}C-NMR (500 MHz, solid state): δ 4.97, 28.42, 41.01, 46.9, 49.5, 59.57, 71.69, 83.87 (C-2), 129.67.

Method 3b: To a solution of (1*R*,2*S*)-*N*-aminoephedrine (0.30 g, 1.7 mmol) in dry benzene (30 ml), 1-benzylpiperidin-4-one (0.31 g, 1.6 mmol) was

added, followed by a few drops of ethanol containing 22% hydrogen chloride. The reaction mixture was stirred at room temperature for 6 hours, and then evaporated to dryness. The residue was dissolved in 5 ml ethanol containing 22% hydrogen chloride, after a few minutes the solution was evaporated to dryness and the residue was crystallized from an ethanol/diethyl ether mixture. ^{13}C-NMR: see Method 3a.

Example 4

(3R,4S)-2,3-Dimethyl-4-phenyl-5-oxa-1,2-diazaspiro[5.5]undecane hydrochloride

The title compound was synthesized using each of the following four synthetic methods.

Method 4a: To a solution of (1*S*,2*R*)-*N*-aminoephedrine (0.30 g, 1.7 mmol) in dry benzene (40 ml), cyclohexanone (0.83 g, 8.5 mmol) was added. The reaction mixture was left to stand at room temperature for 6 hours, and then evaporated to dryness. The residue was dissolved in 5 ml ethanol containing 22% hydrogen chloride, after a few minutes the solution was evaporated to dryness and the semisolid residue was crystallized from an ethanol/diethyl ether mixture. ^{13}C-NMR (500 MHz, solid state): δ 4.28, 24.0 (broad), 38.25, 45.05, 58.98, 70.53, 87.5 (C-2), 129.67.

Method 4b: To a solution of (1*S*,2*R*)-*N*-aminoephedrine (0.30 g, 1.7 mmol) in dry benzene (40 ml) cyclohexanone (0.83 g, 8.5 mmol) and a catalytic amount (some crystals) of *p*-toluenesulfonic acid were added. The reaction mixture was left to stand at room temperature for 6 hours, and then evaporated to dryness. The residue was dissolved in 5 ml ethanol containing 22% hydrogen chloride, after a few minutes the solution was evaporated to dryness and the semisolid residue was crystallized from an ethanol/diethyl ether mixture. ^{13}C-NMR: see Method 4a.

Method 4c: To a solution of (1*S*,2*R*)-*N*-aminoephedrine (0.30 g, 1.7 mmol) in dry benzene (40 ml), cyclohexanone (0.83 g, 8.5 mmol) and Amberlist®

15 ion-exchange resin (0.1 g) were added. The reaction mixture was stirred at room temperature for 5 hours, the ion-exchange resin was then filtered off and the filtrate was evaporated to dryness. The residue was dissolved in 5 ml ethanol containing 22% hydrogen chloride, after a few minutes the solution was evaporated to dryness and the semisolid residue was crystallized from an ethanol/diethyl ether mixture. ^{13}C-NMR: see Method 4a.

Method 4d: To a solution of (1*S*,2*R*)-*N*-aminoephedrine (0.30 g, 1.7 mmol) in dry methylene chloride (25 ml), cyclohexanone (0.83 g, 8.5 mmol) and anhydrous magnesium sulfate (5 g) were added. The reaction mixture was stirred at room temperature for 10 hours, the magnesium sulfate was then filtered off and the filtrate was evaporated to dryness. The residue was dissolved in 5 ml ethanol containing 22% hydrogen chloride, after a few minutes the solution was evaporated to dryness and the semisolid residue was crystallized from an ethanol/diethyl ether mixture. ^{13}C-NMR: see Method 4a.

Example 5

(4aR,8aS*)-4-Methyl-2,2-pentamethylene-3,4,4a,5,6,7,8,8a-octahydro-2H-1,3,4-benzoxadiazine hydrochloride*

The title compound was synthesized using each of the following three synthetic methods.

Method 5a: To a solution of 1-oxa-2-azaspiro[2.5]octane (0.60 g, 5.3 mmol) in diethyl ether (20 ml), a solution of *cis*-2-(methylamino)cyclohexanol (0.68 g, 5.3 mmol) in diethyl ether (5 ml) was added. The reaction mixture was stirred at room temperature for 30 minutes and then evaporated to dryness. The residue was dissolved in 5 ml ethanol containing 22% hydrogen chloride, after a few minutes the solution was evaporated to dryness and the semisolid residue was crystallized from an ethanol/diethyl ether mixture. ^{13}C-NMR (500 MHz, solid state): δ 24.01 (broad), 42.6, 60.1, 65.9, 86.86 (C-2).

Method 5b: To a solution of *cis*-2-(*N'*-methylhydrazino)cyclohexanol (0.43 g, 3 mmol) in dry benzene (40 ml), cyclohexanone (1.47 g, 15 mmol) and molecular sieve 4Å (8 g) were added. The reaction mixture was stirred at room

temperature for 10 hours, the molecular sieve was then filtered off and the filtrate was evaporated to dryness. The residue was dissolved in 5 ml ethanol containing 22% hydrogen chloride, after a few minutes the solution was evaporated to dryness and the semisolid residue was crystallized from an ethanol/diethyl ether mixture. ^{13}C-NMR: see Method 5a.

Method 5c: To a solution of *cis*-2-(N^1-methylhydrazino)cyclohexanol (0.43 g, 3 mmol) in dry toluene (40 ml), cyclohexanone (1.47 g, 15 mmol) and silica gel (0.035-0.07 mm, 2 g) were added. The reaction mixture was stirred at room temperature for 8 hours, the silica gel was then filtered off and the filtrate was evaporated to dryness. The residue was dissolved in 5 ml ethanol containing 22% hydrogen chloride, after a few minutes the solution was evaporated to dryness and the semisolid residue was crystallized from an ethanol/diethyl ether mixture. ^{13}C-NMR: see Method 5a.

Example 6

(4aR,8aR*)-2,2,4-Trimethyl-3,4,4a,5,6,7,8,8a-octahydro-2H-1,3,4-benzoxadiazine hydrochloride*

The title compound was synthesized using each of the following two synthetic methods.

Method 6a: A solution of *trans*-2-(N^1-methylhydrazino)cyclohexanol (0.35 g, 2.4 mmol) in dry acetone (40 ml) was left to stand at room temperature for 6 hours. The solution was then evaporated to dryness and 5 ml ethanol containing 22% hydrogen chloride was added. After a few minutes, the solution was evaporated to dryness and the residue was recrystallized from an ethanol/diethyl ether mixture. ^{13}C-NMR (500 MHz, solid state): δ 21.2, 25.2, 27.6, 31.5, 42.3, 68.5, 74.3, 88.46 (C-2).

Method 6b: A solution of a mixture of *trans*-2-(N^1-methylhydrazino)cyclohexanol (0.35 g, 2.4 mmol) in dry acetone (40 ml) and a catalytic amount of ethanol containing 22% hydrogen chloride (1 drop) was left to stand at room temperature for 72 hours. The solution was then evaporated to

dryness and the residue was recrystallized from a methanol/diethyl ether mixture. ^{13}C-NMR: see Method 6a.

Example 7

(4aR,8aR*)-4-Benzyl-2-ethyl-2methyl-3,4,4a,5,6,7,8,8a-octahydro-2H-1,3,4-benzoxadiazine hydrochloride*

Method 7a: To a solution of *trans*-2-(N^1-benzylhydrazino)cyclohexanol (0.66 g, 3 mmol) in 2-butanone (25 ml), a catalytic amount of oxalic acid was added. The reaction mixture was left to stand at room temperature for 24 hours and then evaporated to dryness. The pale-yellow oily product was dissolved in methanol (2 ml) and was converted to the crystalline dihydrochloride salt by using ethanol containing 22% hydrogen chloride (1 ml) and diethyl ether. The crystals were filtered off and recrystallized from methanol/diethyl ether. ^{13}C-NMR (500 MHz, solid state): δ 7.98, 16.9, 23.4, 26.2, 30.1, 59.9, 67.2, 90.49 (C-2), 128.1, 139.3.

Example 8

2,2-Dimethyl-1,2,4a,5-tetrahydro-4H,10H-1,3,4-oxadiazino[4,5-b]isoquinoline hydrochloride

The title compound was synthesized using each of the following three synthetic methods.

Method 8a: To a solution of 2-amino-1,2,3,4-tetrahydroisoquinoline 3-methanol (0.53 g, 3 mmol) in 2,2-dimethoxypropane (25 ml), a catalytic amount of *p*-toluenesulfonic acid was added. The reaction mixture was left to stand at room temperature for 24 hours and then evaporated to dryness. The pale-yellow oily product was dissolved in methanol (2 ml) and was converted to the crystalline dihydrochloride salt by using ethanol containing 22% hydrogen chloride (1 ml) and diethyl ether. The crystals were filtered off and recrystallized from methanol/diethyl ether. ^{13}C-NMR (500 MHz, solid state): δ 15.1, 20.7, 27.8, 56.14, 63.0, 89.90 (C-2), 127.4, 130.1.

Method 8b: To a solution of 2-amino-1,2,3,4-tetrahydroisoquinoline 3-methanol (0.53 g, 3 mmol) in dry acetone (25 ml), a catalytic amount of L-tartaric acid (a few crystals) was added. The reaction mixture was left to stand at room temperature for 24 hours and then evaporated to dryness. The pale-yellow oily product was dissolved in methanol (2 ml) and was converted to the crystalline dihydrochloride salt by using ethanol containing 22% hydrogen chloride (1 ml) and diethyl ether. The crystals were filtered off and recrystallized from methanol/diethyl ether. ^{13}C-NMR: see Method 8a.

Method 8c: 2-Amino-1,2,3,4-tetrahydroisoquinoline 3-methanol hydrochloride (0.64 g, 3 mmol) was suspended in dry acetone (40 ml). The reaction mixture was stirred at room temperature for 36 hours and then evaporated to dryness. The semisolid residue crystallized on treatment with methanol/diethyl ether. The crystals were filtered off and recrystallized from methanol/diethyl ether. ^{13}C-NMR: see Method 8a.

Example 9

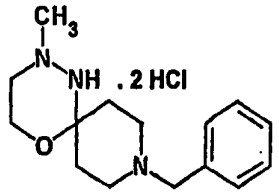
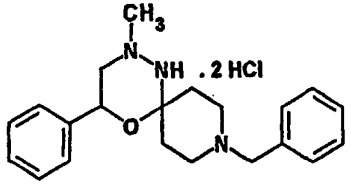
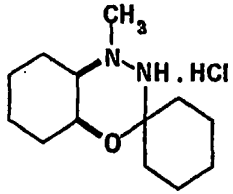
***trans* 2-[1-methyl-2-(4-pyridylmethylene)hydrazino]-1-cyclohexanol**

To a solution of *trans* 2-(1-methylhydrazino)-1-cyclohexanol (0.43 g, 3 mmol) in dry methanol (15 ml) 4-pyridinecarboxaldehyde (0.33 g, 3 mmol) was added. The reaction mixture was left to stand at room temperature for 2 hours then evaporated *in vacou*. The oily residue was crystallized on treatment with a mixture of *n*-hexane and diethyl ether. The separated crystals were filtered off and recrystallized from a mixture of diisopropyl ether and ethyl acetate. The physical data are given in Table 3.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20-1.45 (4H, om, $(CH_2)_4$), 1.77 (2H, m, $(CH_2)_4$), 1.86 (1H, m $(CH_2)_4$), 2.14 (1H, m $(CH_2)_4$), 2.99 (3H, s, NCH_3), 3.10 (2H, m, NC*H*), 3.96 (1H, m, OC*H*), 7.06 (1H, s, N=C*H*), 7.36 (m, 2H, C_5H_4N), 8.47 (m, 2H, C_5H_4N).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 24.7, 25.4, 29.2, 33.9, 36.8, 71.6, 73.7, 119.9 (N=C), 127.2, 150.2.

Table 1. Physical data of the synthesized racemic compounds

Compound	Structure	M.P. (°C)	Yield (%)	Formula (M.W.)	[M+1] (MS)	Elemental analysis Calcd./Found (%) C H N
1		184-188	45 (1a) 38 (1b) 40 (1c)	$C_{15}H_{25}Cl_2N_3O$ 334.29	262	53.90 7.54 12.57 53.84 7.25 12.83
2		186-190	49 (2a) 54 (2b)	$C_{21}H_{29}Cl_2N_3O$ 410.39	338	61.46 7.12 10.24 61.56 7.33 10.58
5		170-174	37 (5a) 43 (5b) 39 (5c)	$C_{13}H_{25}ClN_2O$ (260.81)	225	59.87 9.66 10.74 59.63 9.41 10.58

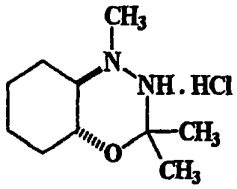
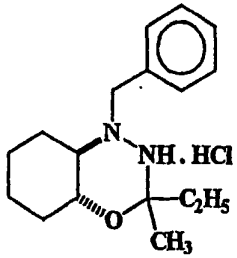
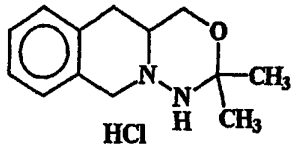
Compound	Structure	M.P. (°C)	Yield (%)	Formula (M.W.)	[M+1]+ (MS)	Elemental analysis Calcd./Found (%) C H N
6		197-201	63 (6a) 68 (6b)	$C_{10}H_{21}ClN_2O$ (220.74)	185	54.41 9.59 12.69 54.26 9.40 12.75
7		175-177	52	$C_{17}H_{27}ClN_2O$ (310.87)	275	65.68 8.75 9.01 65.93 9.00 8.99
8		143-147	74 (8a) 76 (8b) 70 (8c)	$C_{13}H_{19}ClN_2O$ (254.76)	219	61.29 7.52 11.00 61.14 7.37 11.13

Table 2. Physical data of the synthesized enantiomeric compounds

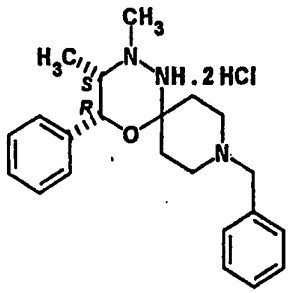
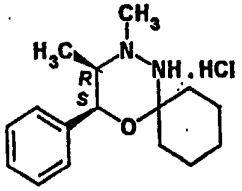
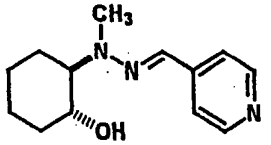
Compound	Structure	Formula (M.w.)	Yield (%)	M.p. (°C)	$[\alpha]_D^{20}$	Elementary analysis (calcd/found) C H N
3		$C_{22}H_{31}Cl_2N_3O$ (424.41)	78 (3a) 72 (3b)	165-168	–55 (CH_3OH, c = 0.11)	62.26 7.36 9.90 62.45 7.43 9.56
4		$C_{16}H_{25}ClN_2O$ (296.84)	48 (4a) 52 (4b) 54 (4c) 50 (4d)	153-158	+65 (CH_3OH, c = 0.11)	64.74 8.49 9.44 64.34 8.65 9.56

Table 3

Number	Structure	M.p. (°C)	Yield (%)	Formula (M.w.)	Elemental analysis Calcd./Found (%)	Synthetic method
9		153-154	73	$C_{13}H_{19}N_3O$ (233.31)	66.92 8.21 18.01 67.18 7.94 17.95	Example 9

Example 10

In Vitro Inhibition of VAP-1 SSAO Activity

VAP-1 SSAO activity was measured using the coupled colourimetric method essentially as described for monoamine oxidase and related enzymes (Holt, A., *et al.*, *Anal. Biochem. 244*:384-392 (1997)). Recombinant human VAP-1 SSAO expressed in Chinese Hamster Ovary (CHO) cells was used as a source of VAP-1 SSAO for activity measurements. Native CHO cells have negligible SSAO activity. These cells and their culture have previously been described (Smith, D.J., *et al.*, *J. Exp. Med. 188*:17-27 (1998)). A cell lysate was prepared by suspending approximately 3.6×10^8 cells in 25ml lysis buffer (150mM NaCl, 10 mM Tris-Base pH 7.2, 1.5 mM $MgCl_2$, 1% NP40, 1% Aprotinin, and 1mM PMSF) and incubating at 4°C overnight on a rotating table. The lysate was clarified by centrifugation at 21200 g for 30 min at 4°C and the supernatant used directly in the assay. The VAP-1 SSAO assay was performed in 96 well microtitre plates as follows. To each well was added a predetermined amount of inhibitor if required. The amount of inhibitor varied in each assay but was generally at a final concentration of between 10 nM and 2.5 mM. Controls lacked inhibitor. The inhibitor was in a total volume of 20 :l in water. The following reagents were then added. 0.2M potassium phosphate buffer pH 7.6 to a total reaction volume of 200µl, 45 µl of freshly made chromogenic solution containing 1mM 2,4-dichlorophenol, 500 µM 4-aminoantipyrine and 4 :g/ml horseradish peroxidase and an amount of CHO cell lysate containing VAP-1 SSAO that caused a change of 0.6 A_{490} per h. This was within the linear response range of the assay. The plates were incubated for 30 min at 37°C and the background absorbance measured at 490 nm using a Wallac Victor II multilabel counter. To initiate the enzyme reaction 20 µl 10mM benzylamine (final concentration = 1mM) was added and the plate incubated for 1 h at 37°C. The increase in absorbance, reflecting VAP-1 SSAO activity, was measured at 490nm. Inhibition was presented as percent inhibition compared to control after correcting for background absorbance.

Example 11

Comparison of VAP-1 SSAO activity versus total human MAO activity

Human MAO was prepared from human liver by homegenising liver samples 1:25 (w/v) in ice-cold potassium phosphate buffer (0.2 M, pH 7.6) with a hand held Ten Broeck homogeniser. After centrifugation at 1000 g and 4°C for 15 min the supernatant was carefully withdrawn and used as the source of MAO. Total MAO activity was measured in a similar way as for VAP-1 SSAO except that 2,4-dichlorophenol was replaced by 1mM vanillic acid. To each well was added a predetermined amount of inhibitor if required. The amount of inhibitor varied in each assay but was generally at a final concentration of between 10 nM and 2.5 mM. Controls lacked inhibitor. The inhibitor was in a total volume of 20 :l in water. The following reagents were then added. 0.2 M potassium phosphate buffer pH 7.6 for a total reaction volume of 300 µl, 50 µl of freshly made chromogenic solution (as above) and 50 µl of MAO preparation. The plates were incubated for 30 min at 37°C and the background absorbance measured at 490 nm using a Wallac Victor II multilabel counter. To initiate the enzyme reaction 20 µl of 5 mM tyramine (final concentration 0.5 mM) was added and the plate incubated for 1 h at 37°C. The increase in absorbance, reflecting MAO activity, was measured at 490nm. Inhibition was presented as percent inhibition compared to control after correcting for background absorbance. Clorgyline and pargyline (inhibitors of MAO-A and –B respectively) at 0.5 µM were added to some wells as positive controls for MAO inhibition.

The ability of compounds of Examples 1 to 8 to inhibit VAP-1 SSAO activity with specificity for VAP-1 SSAO over human MAO is shown in Table 3. The results indicate that the compounds of the invention (or their hydrazino alcohol degradation products) are specific inhibitors of human VAP-1 SSAO activity, and are more potent inhibitors of VAP-1 SSAO than previously known inhibitors of VAP-1 SSAO such as semicarbazide. The compounds of the present invention are therefore expected to have therapeutic utility in the treatment of

diseases and conditions in which the the SSAO activity of the human adhesion molecule VAP-1 plays a role.

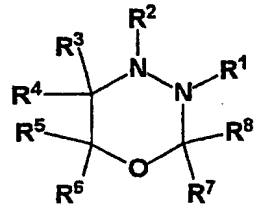
Table 3

Compound	VAP-1 SSAO IC50 uM	Total MAO IC50 um	Selectivity VAP over MAO
1	0.29	124	428
2	0.11	69	627
3	0.08	118	1475
4	0.10	140	1400
5	0.70	211	301
6	0.60	163	272
7	3.80	207	54
8	170.00	275	2

Having now fully described this invention, it will be understood to those of ordinary skill in the art that the same can be performed within a wide and equivalent range of conditions, formulations, and other parameters without affecting the scope of the invention or any embodiment thereof. All patents and publications cited herein are fully incorporated by reference herein in their entirety.

What Is Claimed Is:

1. Use of an oxadiazine compound of Formula *I*:



I

or a tautomer, isomer, hydrazino alcohol degradation product, or a pharmaceutically acceptable solvate, hydrate, or salt thereof; wherein:

R^1 is hydrogen or C_1-C_4 alkyl;

R^2 is hydrogen, C_1-C_4 alkyl, C_2-C_4 alkenyl, aralkyl, C_2-C_6 alkanoyl, C_3-C_6 alkenoyl, or C_7-C_{11} aroyl which is optionally substituted;

R^3, R^4, R^5, and R^6, which can be the same or different, are hydrogen, C_1-C_4 alkyl or optionally substituted aryl;

or any two of said substituents R^3, R^4, R^5, and R^6 are taken together with the carbon atoms to which they are attached to form an optionally substituted carbocyclic or hetercyclic ring;

or R^2 and R^3 are taken together with the atoms to which they are attached to form an optionally substituted carbocyclic or heterocyclic ring; and

R^7 is hydrogen, C_1-C_4 alkyl, aryl, substituted aryl, heteroaryl, or aralkyl; R^8 is C_1-C_4 alkyl, aryl, substituted aryl, heteroaryl, or aralkyl;

or R^7 and R^8 are taken together with the carbon atoms to which they are attached to form an optionally substituted 5-12 membered carbocyclic or heterocyclic ring, for the manufacture of a pharmaceutical preparation for inhibiting copper-containing amine oxidase.

2. The use of a compound as defined in claim 1 for the manufacture of a pharmaceutical preparation for the treatment of an inflammatory disease or condition, a disease related to carbohydrate metabolism, a disease related to aberrations in adipocyte differentiation or function or smooth muscle cell function, or a vascular disease.

3. The use of claim 1 or 2, wherein R^2 is benzyl substituted with alkyl, nitro, methoxy, or halogen.

4. The use of claim 3, wherein R^2 is benzyl substituted at the *para* position with methyl, nitro, methoxy, or chlorine.

5. The use of claim 1 or 2, wherein two of R^3, R^4, R^5 and R^6 are taken together with the carbon atoms to which they are attached to form a 5-7 membered carbocyclic or heterocyclic ring.

6. The use of claim 5, wherein R^4 and R^6 are taken together with the carbon atoms to which they are attached to form a 5-7 membered carbocyclic or heterocyclic ring, and R^3 and R^5 are each hydrogen.

7. The use of claim 6, wherein said 5-7 membered ring is selected from the group consisting of cyclopentane, cyclohexane, 4-methyl–cyclohexane, and cycloheptane.

8. The use of claim 1 or 2, wherein R^2 and R^3 are taken together with the carbon atoms to which they are attached to form an optionally substituted heterocyclic ring.

9. The use of claim 8, wherein the substituents R^2 and R^3 are taken together to form a 5 to 6 membered, saturated, nitrogen-containing heterocyclic ring which is optionally substituted with alkyl.

10. The use of claim 8, wherein R^2 and R^3 are taken together to form an optionally substituted heterocyclic ring selected from the group consisting of 1,2,3,4-tetrahydroquinoline, 1,2,3,4,-tetrahydroisoquinoline, 2,3-dihydroindole, piperidine, and 6,7-dimethoxy-1,2,3,4-tetrahydro–isoquinoline.

11. The use of claim 1 or 2, wherein R^7 and R^8 are taken together to form an optionally substituted carbocyclic or heterocyclic ring.

12. The use of claim 11, wherein said carbocyclic or heterocyclic ring is substituted with alkyl, aralkyl, or substituted aralkyl.

13. The use of claim 12, wherein said carbocyclic or heterocyclic ring is N-benzylpiperidine.

14. The use of claim 2, wherein said inflammatory disease or condition is a connective tissue inflammatory disease or condition.

15. The use of claim 14, wherein said connective tissue inflammatory disease or condition is selected from the group consisting of ankylosing spondylitis, Reiter's syndrome, psoriatic arthritis, osteoarthritis or degenerative joint disease, rheumatoid arthritis, Sjögren's syndrome, Behçet's syndrome, relapsing polychondritis, systemic lupus erythematosus, discoid lupus erythematosus, systemic sclerosis, eosinophilic fasciitis, polymyositis and dermatomyositis, polymyalgia rheumatica, vasculitis, temporal arteritis, polyarteritis nodosa, Wegener's granulomatosis, mixed connective tissue disease, and juvenile rheumatoid arthritis.

16. The use of claim 2, wherein said inflammatory disease or condition is a gastrointestinal inflammatory disease or condition.

17. The use of claim 16, wherein said gastrointestinal inflammatory disease or condition is selected from the group consisting of Crohn's disease, ulcerative colitis, irritable bowel syndrome (spastic colon), fibrotic conditions of the liver, inflammation of the oral mucosa (stomatitis), and recurrent aphtous stomatitis.

18. The use of claim 2, wherein said inflammatory disease or condition is a central nervous system inflammatory disease or condition.

19. The use of claim 18, wherein said central nervous system inflammatory disease or condition is selected from the group consisting of multiple sclerosis, Alzheimer's disease, and ischaemia-reperfusion injury associated with ischemic stroke.

20. The use of claim 2, wherein said inflammatory disease or condition is a pulmonary inflammatory disease or condition.

21. The use of claim 20, wherein said pulmonary inflammatory disease or condition is selected from the group consisting of asthma, chronic obstructive pulmonary disease, and adult respiratory distress syndrome.

22. The use of claim 2, wherein said inflammatory disease or condition is a skin inflammatory disease or condition.

23. The use of claim 22, wherein said skin inflammatory disease or condition is selected from the group consisting of contact dermatitis, atopic dermatitis, psoriasis, pityriasis rosea, lichen planus, and pityriasis rubra pilaris.

24. The use of claim 2, wherein said disease related to carbohydrate metabolism is selected from the group consisting of diabetes, atherosclerosis, vascular retinopathies, retinopathy, nephropathy, nephrotic syndrome, polyneuropathy, mononeuropathies, autonomic neuropathy, foot ulcers, joint problems, and increased risk of infection.

25. The use of claim 2, wherein said disease related to aberrations in adipocyte differentiation or function or smooth muscle cell function is selected from the group consisting of atherosclerosis and obesity.

26. The use of claim 2, wherein said vascular disease is selected from the group consisting of atheromatous ateriosclerosis, nonatheromatous ateriosclerosis, ischemic heart disease, peripheral aterial occlusion, thromboangiitis obliterans (Buerger's disease), and Raynaud's disease and phenomenon.

27. The use of claim 1 or 2, wherein said compound of Formula *I* is selected from the group consisting of:
9-benzyl-2-methyl-5-oxa-1,2,9-triazaspiro[5.5]undecane,
9-benzyl-2-methyl-4-phenyl-5-oxa-1,2,9-triazaspiro[5.5]-undecane,
(3*S*,4*R*)-9-benzyl-2,3-dimethyl-4-phenyl-5-oxa-1,2,9-triazaspiro[5.5]undecane,
(3*R*,4*S*)-2,3-dimethyl-4-phenyl-5-oxa-1,2-diazaspiro[5.5]undecane,
(4a*R**,8a*S**)-4-methyl-2,2-pentamethylene-3,4,4a,5,6,7,8,8a-octahydro-2*H*-1,3,4-benzoxadiazine,
(4a*R**,8a*R**)-2,2,4-trimethyl-3,4,4a,5,6,7,8,8a-octahydro-2*H*-1,3,4-benzoxadiazine,

(4a*R**,8a*R**)-4-benzyl-2-ethyl-2methyl-3,4,4a,5,6,7,8,8a-octahydro-2*H*-1,3,4-benzoxadiazine,

2,2-dimethyl-1,2,4a,5-tetrahydro-4*H*,10*H*-1,3,4-oxadiazino[4,5-*b*]isoquinoline, and

2,3-dimethyl-4-phenyl-5-oxa-1,2-diazaspiro[5.5]undecane; or

a pharmaceutically acceptable salt thereof.

28. The use of claim 1 or 2, wherein said compound of Formula *I* is (3*S*,4*R*)-9-benzyl-2,3-dimethyl-4-phenyl-5-oxa-1,2,9-triazaspiro[5.5]undecane, (3*R*,4*S*)-2,3-dimethyl-4-phenyl-5-oxa-1,2-diazaspiro[5.5]undecane, or a pharmaceutically acceptable salt thereof.

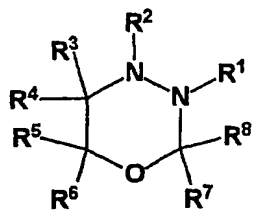
29. A method of inhibiting a copper-containing amine oxidase, comprising contacting said amine oxidase with an inhibitory effective amount of a 1,3,4-oxadiazine compound of Formula *I* as defined in any of the claims 1 to 28.

30. The method of claim 29, wherein said contacting occurs *in vitro*.

31. The method of claim 29, wherein said contacting occurs *in vivo*.

32. A method of treating an inflammatory disease or condition, a disease related to carbohydrate metabolism, a disease related to aberrations in adipocyte differentiation or function or smooth muscle cell function, or a vascular disease, comprising administering to an animal in need or such treatment or prevention an effective amount of an oxadiazine compound of Formula *I* as defined in any on of the claims 1 to 28.

33. A compound of Formula *I*:



I

or a tautomer, isomer, or a pharmaceutically acceptable solvate, hydrate, or salt thereof, wherein:

R^1 is hydrogen, or (C_1-C_4)alkyl;

R^2 is hydrogen, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_6-C_{10} ar(C_1-C_4)alkyl, C_2-C_6 alkanoyl, C_2-C_6 alkenoyl, or benzoyl, any of which may be optionally substituted with C_1-C_4 alkyl, nitro, methoxy or halogen;

R^3, R^4, R^5, and R^6, which can be the same or different, are hydrogen, or C_1-C_4 alkyl or C_6-C_{10} aryl, either of which is optionally substituted with C_1-C_4 alkyl or halogen;

or two of said substituents R^3, R^4, R^5 and R^6 are taken together with the carbon atoms to which they are attached to form a 5 to 12 membered carbocyclic or heterocyclic ring optionally substituted with C_1-C_4 alkyl or halogen;

or R^2 and R^3 are taken together with the atoms to which they are attached to form a 5 to 12 membered carbocyclic or heterocyclic ring optionally substituted with C_1-C_6 alkyl or halogen; and

R^7 is hydrogen, C_1-C_4 alkyl, C_6-C_{10} aryl, substituted C_6-C_{10} aryl, heteroaryl, or C_6-C_{10} ar(C_1-C_4)alkyl;

R^8 is C_1-C_4 alkyl, C_6-C_{10} aryl, substituted C_6-C_{10} aryl, heteroaryl, or C_6-C_{10} ar(C_1-C_4)alkyl;

or R^7 and R^8 are taken together with the carbon atoms to which they are attached to form a 5-12 membered carbocyclic or heterocyclic ring optionally substituted with C_1-C_6 alkyl, or C_6-C_{10} ar(C_1-C_4)alkyl;

provided that R^3 and R^4 are not hydrogen or C_1-C_4 alkyl when R^7 and/or R^8 are C_1-C_4 alkyl or optionally substituted phenyl, or when R^7 and R^8 are taken together with the carbon atom to which they are attached to form an unsubstituted C_5-C_7 cycloalkyl group.

34. The compound of claim 33, wherein R^2 is benzyl substituted with alkyl, nitro, methoxy, or halogen.

35. The compound of claim 34, wherein R^2 is benzyl substituted at the *para* position with methyl, nitro, methoxy, or chlorine.

36. The compound of claim 33, wherein two of R^3, R^4, R^5 and R^6 are taken together with the carbon atoms to which they are attached to form a 5-7 membered carbocyclic or heterocyclic ring.

37. The compound of claim 36, wherein R^4 and R^6 are taken together with the carbon atoms to which they are attached to form a 5-7 membered carbocyclic or heterocyclic ring, and R^3 and R^5 are each hydrogen.

38. The compound of claim 37, wherein said 5-7 membered ring is selected from the group consisting of cyclopentane, cyclohexane, 4-methyl–cyclohexane, and cycloheptane.

39. The compound of claim 33, wherein R^2 and R^3 are taken together with the carbon atoms to which they are attached to form an optionally substituted heterocyclic ring.

40. The compound of claim 39, wherein the substituents R^2 and R^3 are taken together to form a 5 to 6 membered, saturated, nitrogen-containing heterocyclic ring which is optionally substituted with alkyl.

41. The compound of claim 39, wherein R^2 and R^3 are taken together to form an optionally substituted heterocyclic ring selected from the group consisting of 1,2,3,4-tetrahydroquinoline, 1,2,3,4,-tetrahydroisoquinoline, 2,3-dihydroindole, piperidine, and 6,7-dimethoxy-1,2,3,4-tetrahydro–isoquinoline.

42. The compound of claim 33, wherein R^7 and R^8 are taken together to form an optionally substituted carbocyclic or heterocyclic ring.

43. The compound of claim 42, wherein said carbocyclic or heterocyclic ring is substituted with alkyl, aralkyl, or substituted aralkyl.

44. The compound of claim 43, wherein said carbocyclic or heterocyclic ring is N-benzylpiperidine.

45. A compound of claim 33, which is selected from the group consisting of:

9-benzyl-2-methyl-5-oxa-1,2,9-triazaspiro[5.5]undecane,

9-benzyl-2-methyl-4-phenyl-5-oxa-1,2,9-triazaspiro[5.5]-undecane, (3*S*,4*R*)-9-benzyl-2,3-dimethyl-4-phenyl-5-oxa-1,2,9-triazaspiro[5.5]undecane,

(4a*R**,8a*S**)-4-methyl-2,2-pentamethylene-3,4,4a,5,6,7,8,8a-octahydro-2*H*-1,3,4-benzoxadiazine,

(4a*R**,8a*R**)-2,2,4-trimethyl-3,4,4a,5,6,7,8,8a-octahydro-2*H*-1,3,4-benzoxadiazine,

(4a*R**,8a*R**)-4-benzyl-2-ethyl-2methyl-3,4,4a,5,6,7,8,8a-octahydro-2*H*-1,3,4-benzoxadiazine, and

2,2-dimethyl-1,2,4a,5-tetrahydro-4*H*,10*H*-1,3,4-oxadiazino[4,5-*b*]isoquinoline;

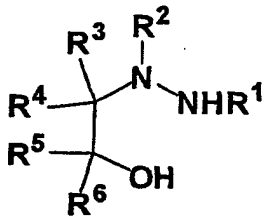
or a pharmaceutically acceptable salt thereof.

46. A pharmaceutical composition comprising a compound of any one of claims 33-45 and a pharmaceutically acceptable carrier or diluent.

47. A compound of any one of the claims 33-45 for therapeutical use.

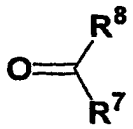
48. A process for preparing a 1,3,4-oxadiazine compound of claim 33, comprising:

reacting a hydrazino alcohol of Formula II:



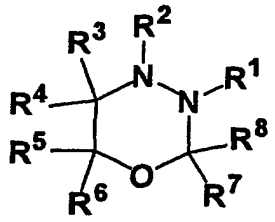
II

with a ketone of Formula IV:



IV

to form a 1,3,4-oxadiazine of Formula I:



I

or a tautomer, isomer, solvate, hydrate, or pharmaceutically acceptable salt thereof, wherein:

R^1 is hydrogen, or (C_1-C_4)alkyl;

R^2 is hydrogen, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_6-C_{10} ar(C_1-C_4)alkyl, C_2-C_6 alkanoyl, C_2-C_6 alkenoyl, or benzoyl, any of which may be optionally substituted with C_1-C_4 alkyl, nitro, methoxy or halogen;

R^3, R^4, R^5, and R^6, which can be the same or different, are hydrogen, or C_1-C_4 alkyl or C_6-C_{10} aryl, either of which is optionally substituted with C_1-C_4 alkyl or halogen;

or two of said substituents R^3, R^4, R^5 and R^6 are taken together with the carbom atoms to which they are attached to form a 5 to 12 membered carbocyclic or heterocyclic ring optionally substituted with C_1-C_4 alkyl or halogen;

or R^2 and R^3 are taken together with the atoms to which they are attached to form a 5 to 12 membered carbocyclic or heterocyclic ring optionally substituted with C_1-C_6 alkyl or halogen; and

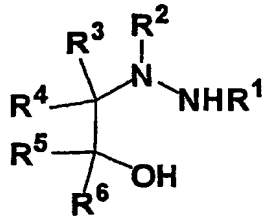
R^7 is hydrogen, C_1-C_4 alkyl, C_6-C_{10} aryl, substituted C_6-C_{10} aryl, heteroaryl, or C_6-C_{10} ar(C_1-C_4)alkyl;

R^8 is C_1-C_4 alkyl, C_6-C_{10} aryl, substituted C_6-C_{10} aryl, heteroaryl, or C_6-C_{10} ar(C_1-C_4)alkyl;

or R^7 and R^8 are taken together with the carbon atoms to which they are attached to form a 5-12 membered carbocyclic or heterocyclic ring optionally substituted with C_1-C_6 alkyl, or C_6-C_{10} ar(C_1-C_4)alkyl.

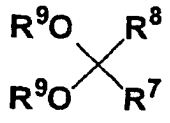
49. A process for preparing a 1,3,4-oxadiazine compound of claim 33, comprising:

reacting a hydrazino alcohol of formula II:



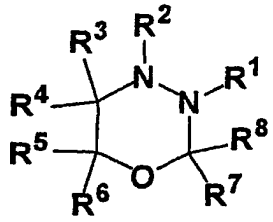
II

with an acetal of Formula V:



V

to form a 1,3,4-oxadiazone of Formula I:



I

or a tautomer, isomer, solvate, hydrate, or pharmaceutically acceptable salt thereof, wherein:

R^1 is hydrogen, or (C_1-C_4)alkyl;

R^2 is hydrogen, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_6-C_{10} ar(C_1-C_4)alkyl, C_2-C_6 alkanoyl, C_2-C_6 alkenoyl, or benzoyl, any of which may be optionally substituted with C_1-C_4 alkyl, nitro, methoxy or halogen;

R^3, R^4, R^5, and R^6, which can be the same or different, are hydrogen, or C_1-C_4 alkyl or C_6-C_{10} aryl, either of which is optionally substituted with C_1-C_4 alkyl or halogen;

or two of said substituents R^3, R^4, R^5 and R^6 are taken together with the carbom atoms to which they are attached to form a 5 to 12 membered carbocyclic or heterocyclic ring optionally substituted with C_1-C_4 alkyl or halogen;

or R^2 and R^3 are taken together with the atoms to which they are attached to form a 5 to 12 membered carbocyclic or heterocyclic ring optionally substituted with C_1-C_6 alkyl or halogen; and

R^7 is hydrogen, C_1-C_4 alkyl, C_6-C_{10} aryl, substituted C_6-C_{10} aryl, heteroaryl, or C_6-C_{10} ar(C_1-C_4)alkyl;

R^8 is C_1-C_4 alkyl, C_6-C_{10} aryl, substituted C_6-C_{10} aryl, heteroaryl, or C_6-C_{10} ar(C_1-C_4)alkyl;

or R^7 and R^8 are taken together with the carbon atoms to which they are attached to form a 5-12 membered carbocyclic or heterocyclic ring optionally substituted with C_1-C_6 alkyl, or C_6-C_{10} ar(C_1-C_4)alkyl.

50. The process of claim 48 or claim 49, wherein said reacting is done in the presence of an acid or base catalyst.

51. The process of claim 48 or claim 49, wherein said reacting is done in the presence of an adsorbent of water.

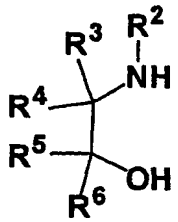
52. The process of claim 50, wherein said acidic catalyst is hydrochloric, *p*-toluenesulfonic, acetic, tartaric or oxalic acid.

53. The process of claim 50, wherein said acidic catalyst is an acid ion-exchange resin suitable for non-aqueous catalysis.

54. The process of claim 50, wherein said basic catalyst is triethylamine.

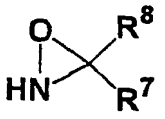
55. A process for preparing a 1,3,4-oxadiazine compound of claim 33, comprising:

reacting an amino alcohol of Formula III:



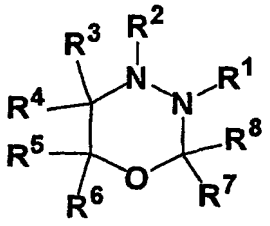
III

with an oxaziridine of Formula VI:



VI

to form a 1,3,4-oxadiazine of Formula I:



I

or a tautomer, isomer, solvate, hydrate, or pharmaceutically acceptable salt thereof, wherein:

R^1 is hydrogen, or (C_1-C_4)alkyl;

R^2 is hydrogen, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_6-C_{10} ar(C_1-C_4)alkyl, C_2-C_6 alkanoyl, C_2-C_6 alkenoyl, or benzoyl, any of which may be optionally substituted with C_1-C_4 alkyl, nitro, methoxy or halogen;

R^3, R^4, R^5, and R^6, which can be the same or different, are hydrogen, or C_1-C_4 alkyl or C_6-C_{10} aryl, either of which is optionally substituted with C_1-C_4 alkyl or halogen;

or two of said substituents R^3, R^4, R^5 and R^6 are taken together with the carbom atoms to which they are attached to form a 5 to 12 membered carbocyclic or heterocyclic ring optionally substituted with C_1-C_4 alkyl or halogen;

or R^2 and R^3 are taken together with the atoms to which they are attached to form a 5 to 12 membered carbocyclic or heterocyclic ring optionally substituted with C_1-C_6 alkyl or halogen; and

R^7 is hydrogen, C_1-C_4 alkyl, C_6-C_{10} aryl, substituted C_6-C_{10} aryl, heteroaryl, or C_6-C_{10} ar(C_1-C_4)alkyl;

R^8 is C_1-C_4 alkyl, C_6-C_{10} aryl, substituted C_6-C_{10} aryl, heteroaryl, or C_6-C_{10} ar(C_1-C_4)alkyl;

or R^7 and R^8 are taken together with the carbon atoms to which they are attached to form a 5-12 membered carbocyclic or heterocyclic ring optionally substituted with C_1-C_6 alkyl, or C_6-C_{10} ar(C_1-C_4)alkyl.

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WO 02/02541 A3

(54) Title: INHIBITORS OF COPPER-CONTAINING AMINE OXIDASES

(57) Abstract: The present invention is directed to 1,3,4-oxadiazine compounds that function as inhibitors of copper-containg amine oxidases commonly known as semicarbazide-sensitive amine oxidases (SSAO), including the human SSAO known as Vascular Adhesion Protein-1 (VAP-1). These SSAO inhibitors have therapeutic utility as drugs to treat conditions and diseases including, but not limited to, a number of inflammatory conditions and diseases (in particular chronic inflammatory conditions such as chronic arthritis, inflammatory bowel diseases, and chronic skin dermatoses), diseases related to carbohydrate metabolism and to abberations in adipocyte differentiation or function and smooth muscle cell function, and vascular diseases. The compounds have the general formula (I): or a tautomer, isomer, hydrazino alcohol degradation product, or a pharmaceutically acceptable solvate, hydrate, or salt thereof, wherein R^1, R^2, R^3, R^4, R^5,R^6, R^7, and R^8 are as defined her ein.

IN ERNATIONAL SEARCH REPORT

International Application No
PCT/FI 01/00637

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D273/04 C07D498/10 C07D498/04 A61K31/5395 A61P43/00
A61P29/00 A61P1/04 A61P17/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
PAJ, CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE STN INTERNATIONAL, CAPLUS [Online] GRIFANTINI M ET AL : "Derivatives of N-amino-1-ephedrine and N-amino-d-pseudoephedrine having antidepressive activity." retrieved from CAPLUS Database accession no. 1968:426896 XP002902241 Document no 69:26896 abstract & FARMACO ,ED. SCI., vol. 23, no. 3, 1968, pages 197-203, --- -/--	1-55

[X] Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search	Date of mailing of the international search report
11 January 2002	20. 02. 2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gerd Strandell

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE STN INTERNATIONAL, CAPLUS [Online] TAKAHASHI H ET AL : "Synthesis of N-alkylaminoephedrines and their effect on bronchinal musculature." retrieved from CAPLUS Database accession no. 1982:142348 XP002902242 Document no. 96:142348 abstract & YAKUGAKU ZASSHI, vol. 101, no. 12, 1981, pages 1154-1156, ---	1-55
X	TREPANIER D L ET AL: "Synthesis and pharmacological evaluation of some tetrahydrooxadiazinones and some dihydroaminooxadiazines." JOURNAL OF MEDICINAL CHEMISTRY, vol. 11, no. 2, 1968, pages 357-360, XP002902243 the whole document ---	1-55
X	US 3 377 345 A (TREPANIER D L ET AL) 9 April 1968 (1968-04-09) the whole document ---	1-55
X	LIZCANO J M ET AL: "Inhibition of bovine lung semicarbazide-sensitive amine oxidase (SSAO) by some hydrazine derivatives." BIOCHEMICAL PHARMACOLOGY, vol. 52, no. 2, 1996, pages 187-195, XP002902244 the whole document ---	1-55
A	WO 93 23023 A (UNIV SASKATCHEWAN ;YU PETER H (CA); ZUO DONG MEI (CA)) 25 November 1993 (1993-11-25) claims 1,2,5,6,9,10,13,16,19 ---	1-55
A	IOFFE B V ET AL: "Über eine neue Art von Ring-Ketten-Tautomerie und die einfachsten Tetrahydro-1,3,4-Oxadiazinderivate. " TETRAHEDRON LETTERS, vol. 8, no. 36, 1967, pages 3505-3508, XP002902245 the whole document ---	1-55
A	POTEKHIN A A ET AL: "Ring-chain tautomerism of substituted hydrazones VII. * Substituted 4-tert-butylperhydro-1,3,4-oxadiazines.*" CHEMISTRY OF HETEROCYCLIC COMPOUNDS, no. 11, 1973, pages 1321-1326, XP002902246 the whole document --- -/--	1-55

2

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	POTEKHIN A A ET AL: "Ring-chain tautomerism of substituted hydrazones II. * Derivatives of 1-hydrazino- and 1-(N-alkylhydrazino)-2-propanols.*" CHEMISTRY OF HETEROCYCLIC COMPOUNDS, vol. 7, no. 3, 1971, pages 277-283, XP002902247 the whole document ---	1-55
A	SCHMITZ E ET AL: "Versuche zur N-Aminierung von Alkaloiden." LIEBIGS ANN. CHEM., 1983, pages 1043-1046, XP002902248 the whole document -----	1-55

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 01/00637

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1 , 29 all in part
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [X] Claims Nos.: 29-32
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Claims Nos.: 1 , 29 all in part

Claims 1, 29 all in part, relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body / Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds / compositions.

Continuation of Box I.2

Claims Nos.: 29-32

The wording " copper-containing amine oxidase " is too broadly formulated to permit a meaningful search. Therefore, the search has been incomplete. See PCT, Article 6.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

IN .RNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/FI 01/00637

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 3377345 A	09-04-1968	NONE	
WO 9323023 A	25-11-1993	CA 2068745 A1	16-11-1993
		CA 2068927 A1	20-11-1993
		AU 4055593 A	13-12-1993
		WO 9323023 A1	25-11-1993
		EP 0639972 A1	01-03-1995